Insulin Like Growth Factor System: How Does it Affect Neonatal Anthropometry?

İnsülin Benzeri Büyüme Faktörü Sistemi Neonatal Antropometriyi Nasıl Etkilemektedir?

Insulin Like Growth Factor System in Fetal Growth

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Özet

Amaç: İnsülin benzeri büyüme faktörü-1 (IGF-1), insulin benzeri büyüme faktörü bağlayıcı proteini-3 (IGFBP-3), insulin ve ghrelinin fetal büyümedeki rolünün değerlendirilmesi amaçlanmıştır. Gereç ve Yöntem: Türk standartları kullanılarak 60 yenidoğan bebek, gestasyonel yaşa göre küçük (SGA) (n=14), gestasyonel yaşa uygun (AGA) (n=33) ve gestasyonel yaşa göre büyük (LGA) (n=13) olarak gruplandırıldı. Maternal serumda ve umbilikal kordon kanında IGF-1, IGFBP-3, ghrelin, and insulin düzeyleri ölçüldü. Bulgular: SGA grubuyla karşılaştırıldığında, LGA grubunda maternal serum ve umbilikal kordon kanındaki IGF-1, IGFBP-3, ghrelin, and insulin düzeyleri anlamlı olarak yüksekti Hem maternal serumdaki hem umbilikal kord kanındaki IGF-1 ve IGFBP-3 düzeylerinin yenidoğanların ağırlığı ve uzunluğuyla, kafa ve karın çevresi ölçümleriyle istatistiksel olarak anlamlı ve pozitif korelasyon gösterdiği saptandı. Tartışma: Bu çalışmadan elde edilen bulgular, insülin benzeri büyüme faktörü sisteminin fetal büyümede rol aldığını düşündürmektedir.

Anahtar Kelimeler

Antropometry; Ghrelin; İnsulin; İnsulin Benzeri Büyüme Faktörü-1; İnsulin Benzeri Büyüme Faktörü Bağlayıcı Proteini-3; Yenidoğan

Abstract

Aim: The present study aims to clarify the role of insulin like growth factor-1 (IGF-1), insulin like growth factor binding protein-3 (IGFBP-3), ghrelin, and insulin in fetal growth. Material and Method: Based on Turkish standards, 14 newborns were defined as small for gestational age (SGA), 33 newborns were described as appropriate for gestational age (AGA), and 13 newborns were identified as large for gestational age (LGA). IGF-1, IGFBP-3, ghrelin, and insulin levels were measured in umbilical cord and maternal serum. Results: The LGA group had significantly higher levels of IGF-1, IGFBP-3, ghrelin, and insulin in umbilical cord and maternal serum than the SGA group. Umbilical cord and maternal serum levels of IGF-1 and IGFBP-3 correlated significantly and positively with body weight, body length, head circumference, and abdominal circumference of the neonates. Discussion: Based on the findings of the present study, it may be postulated that insulin like growth factor system has a role in fetal growth.

Keywords

Anthropometry; Ghrelin; Insulin; Insulin Like Growth Factors; Insulin Like Growth Factor Binding Proteins; Newborn

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Introduction

Insulin, insulin like growth factors (IGFs), and insulin like growth factor binding proteins (IGFBPs) have been established as the main endocrine regulators of fetal growth. The IGFs in maternal circulation regulate fetal tissue growth and metabolism by means of controlling the availability of nutrients to the mother and fetus. Maternal IGFs also play significant roles in placental development, substrate transport, and hormone secretion [1-6]. Ghrelin is a peptide hormone produced by ghrelinergic cells in the gastrointestinal tract. This "hunger hormone" acts as a signal which points out the status of nutrition and energy storage to the feeding center located within the hypothalamus. Ghrelin has also been addressed as an essential element of the endocrine system that controls fetal growth. Ghrelin acts as a signal which points out the status of nutrition and energy storage to the feeding center located within the hypothalamus. Circulating concentrations of ghrelin have been determined in healthy individuals but there are still limited data about the relative role of maternal and fetal ghrelin in the growth process within the uterus [7, 8].

Fetal growth restriction is associated with increased perinatal morbidity and mortality. Moreover, former infants with a history of fetal growth restriction have a greater risk of developing degenerative diseases in adult life. That is why understanding the role of insulin, ghrelin, and the IGF system in fetal growth is essential for the identification of the mechanisms underlying fetal growth restriction [9, 10].

The present study aims to clarify the role of IGF-1, IGFBP-3, ghrelin, and insulin in fetal growth by investigating how anthropometric measurements of the newborns are related with the levels of these endocrinological markers in both maternal serum and the umbilical cord.

Material and Method

This observational study was approved by the Institutional Review Board and Ethical Committee of Kahramanmaras Sutcu Imam University Hospital where it was conducted between September 2012 and December 2012. Written informed consent was obtained from each participant.

The study population consisted of 102 women with term pregnancies who were enrolled over a 3-month-long period at the Perinatology Unit of the study center. Ten mothers who did not want to participate in this study and four mothers who did not have a history of antenatal care in the last trimester of pregnancy were excluded from the study. Five women with multiple gestation, five women with chronic and gestational diseases, and one woman with clinically evident intraamniotic infection were also excluded. Since oral and intravenous glucose administration can decrease serum ghrelin levels, five women who received dextrose solutions during labor were excluded from this study.

Three mothers who delivered newborns with chromosomal abnormalities, two mothers who gave birth to newborns with congenital anomalies, two mothers who delivered newborns with perinatal infections, three mothers who gave birth to newborns that required intensive care treatment in the immediate postnatal period, and two mothers whose newborns had conflicting anthropometric measurements and fetal biometry were excluded from the study. Therefore, 60 mothers and their newborns were found eligible for final analysis. The Turkish standards for sex, gestational age, and birth weight were used to categorize the newborns of the study cohort. Accordingly, 14 newborns were described as small for gestational age (SGA), 33 newborns were identified as appropriate for gestational age (AGA), and 13 newborns were defined as large for gestational age (LGA) at birth [11].

Venous blood samples were obtained from the antecubital area of each participant by phlebotomy between the hours of 08:00 and 09:00 following 10-12 hours of fasting. Blood samples from the umbilical cord were acquired as soon as the participants delivered their newborns. After procurement, these samples were allowed to clot and were exposed to centrifugation for 10 minutes at 3000 g. Then the sera were separated and stored at –70°C until laboratory studies would be performed.

Immunoradiometric assay was used to determine the serum concentrations of IGF-1 (Immunotech, Beckman-Coulter Inc., CA, USA), and serum levels of IGFBP-3 (DRG Diagnostica, Marburg, Germany). Radioimmunassay was used to measure serum concentrations of ghrelin (DRG Diagnostica, Marburg, Germany) and serum levels of insulin (CIS Bio International, Schering AG, Berlin, Germany). The intra-assay coefficients of variation (CVs) were 5.3%, 3.8%, 7.8%, and 6.2% whereas the inter-assay CVs were 1.8%, 1.5%, 10.0%, and 5.7% for IGF-1, IGFBP-3, ghrelin, and insulin respectively.

Collected data were analyzed by Statistical Package for Social Sciences version 18.0 (SPSS IBM Software, Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (range: minimum-maximum) and categorical variables were denoted as numbers or percentages where appropriate. The Smirnov-Kolmogorov test was used to test the distribution of variables. One-way analysis of variance, Mann Whitney U test, and Kruskal-Wallis test were used for the comparisons. A post hoc analysis was carried out to make a retrospective power analysis and it was determined that a cohort size of 60 newborns (14 SGA newborns, 33 AGA newborns, and 13 LGA newborns) had 57.6% power to detect a difference at the 0.05 significance level. Pearson correlation test was used to detect the correlations among the variables. Two-tailed p values less than 0.05 were accepted to be statistically significant.

Results

Table 1 displays the demographic and clinical characteristics of the reviewed infants. When compared with the SGA group, the LGA group had significantly higher body weight (p=0.001), longer body length (p=0.045), larger abdominal circumference (p=0.001), and more male newborns (p=0.001).

Table 2 shows the biochemical characteristics of the reviewed infants. When compared with the SGA group, the LGA group had significantly higher maternal serum IGF-1 (p=0.033), IGFBP-3 (p=0.040), ghrelin (p=0.020), insulin (p=0.018) and significantly higher umbilical cord IGF-1 (p=0.001), IGFBP-3 (p=0.001), ghrelin (p=0.024), and insulin (p=0.028).

Maternal serum concentrations of IGF-1 correlated significantly and positively with body weight (r=0.124, p=0.001), body length (r=0.338, p=0.001), head circumference (r=0.225, p=0.001), and abdominal circumference (r=0.188, p=0.001). Maternal

Table 1. Demographic and Clinical Characteristics of the Reviewed Infants

	SGA (n=14)	AGA (n=33)	LGA (n=13)	P value
Body weight (grams)	2456.4 ± 128.7	3342.2 ± 234.5	4067.1 ± 189.0	0.001
Body length (cm)	48.2 ± 24.5	51.3 ± 28.6	53.7 ± 27.5	0.045
HC (cm)	34.4 ± 9.1	35.1 ± 7.2	35.5 ± 8.3	0.812
TC (cm)	31.5 ± 7.4	34.4 ± 6.9	35.2 ± 5.1	0.066
AC (cm)	26.9 ± 6.2	32.2 ± 5.7	34.3 ± 7.1	0.001
Male sex (n)	4 (28.6%)	13 (39.4%)	13 (100.0%)	0.001
Cesarean delivery (n)	7 (50.0%)	22 (66.7%)	8 (61.5%)	0.734

n: Number of patients (%)
HC: Head circumference
TC: Thoracic circumference
AC: Abdominal circumference

Table 2. Biochemical Characteristics of the Reviewed Infants

	SGA (n=14)	AGA (n=33)	LGA (n=13)	P value
Maternal serum IGF-1 (ng/mL)	159.3±44.7	241.4 ±53.5	308.8±64.9	0.033
Maternal serum IGFBP-3 (µg/mL)	1.6 ± 2.2	2.5 ± 1.1	4.6 ± 2.1	0.040
Maternal serum ghrelin (ng/ml)	2.4 ± 1.0	2.5 ± 1.1	6.5 ± 1.9	0.020
Maternal serum insulin (mIU/L)	16.6 ± 1.5	17.4±1.9	25.8 ± 2.2	0.018
Umbilical cord IGF-1 (ng/mL)	29.2 ± 7.4	53.4 ± 25.0	69.6 ± 37.1	0.001
Umbilical cord IGFBP-3 (µg/mL)	0.9 ± 0.6	1.2±0.7	2.4 ± 0.5	0.001
Umbilical cord ghrelin (ng/ml)	3.2 ± 1.5	4.7 ± 2.0	7.6 ± 2.8	0.024
Umbilical cord insulin (mIU/L)	21.2 ± 10.9	25.4 ± 8.3	30.9 ± 15.5	0.028

serum concentrations of IGFBP-3 correlated significantly and positively with body weight (r=0.134, p=0.001), body length (r=0.354, p=0.001), head circumference (r=0.276, p=0.001), and abdominal circumference (r=0.192, p=0.001). Maternal serum concentrations of insulin and ghrelin did not correlate with the anthropometric measurements of the reviewed newborns.

Umbilical cord concentrations of IGF1-1 correlated significantly and positively with body weight (r=0.119, p=0.001), body length (r=0.455, p=0.001), head circumference (r=0.249, p=0.001), and abdominal circumference (r=0.214, p=0.001). Umbilical cord concentrations of IGFBP-3 correlated significantly and positively with body weight (r=0.298, p=0.001), body length (r=0.364, p=0.001), head circumference (r=0.236, p=0.001) and abdominal circumference (r=0.477, p=0.001). Umbilical cord concentrations of insulin and ghrelin did not correlate with the anthropometric measurements of the reviewed newborns.

Discussion

When a fetus is bound to live in an environment with relative deprivation, adaptive mechanisms begin to work. Poor growth may be regarded as one such adaptation, which occurs as a result of certain endocrinological alterations. In other words, an altered growth hormone-IGF system, with relatively low glucose and relatively high ghrelin concentrations, indicate an adaptation for the relative scarcity of nutrients [12, 13].

It has been reported that diminished fetal growth is associated with alterations in the IGF system. Although reduced maternal IGF-1 has been described in some cases of intrauterine growth restriction (IUGR), other studies failed to demonstrate such an association [13]. Similarly, Chiesa et al. [14] were unable to find a relationship between maternal IGF-1 and birth weight within the entire study population of 153 delivering mothers. When the analysis was confined to preterm newborns however, they noticed that maternal IGF-1 was significantly lower in those who gave birth to neonates with IUGR. This finding was attributed to the secondary consequence of placental dysfunction or the adaptation for restricting glucose supply to a hypoxic fetus [14]. IGFBP-3 is the principal carrier of the IGFs existing in maternal and fetal circulation. Being regulated by insulin, IGFBP-3 acts as a positive modulator of fetal growth and even neonatal growth. A Turkish study demonstrated that the effects of accelerated early infant growth on IGF-1/IGFBP-3 axis in SGA-born infants [15]. Another study indicated a significant rise in serum IGFBP-3 concentrations of the mothers who put on excessive weight gain or became obese during pregnancy. This significant increase was found to contribute to the risk of delivering a LGA fetus [16]. In the study of Chiesa et al., the asymmetric LGA newborns had higher insulin and IGFBP-3 concentrations than AGA and symmetric LGA newborns [14].

Mild maternal hyperinsulinemia may also result in the binding of circulating insulin to the IGF-1 receptors due to the structural similarity between the insulin and IGF-1 receptors. Thus, insulin itself may exert direct effects on fetal growth by means of this interaction. On the other hand, insulin can regulate the IGF system by controlling the IGFBP expression. Insulin may also reduce the expression of IGFBPs, regulate IGF bioavailability to high-affinity receptors, and, thus, trigger fetal growth [17, 18].

Maternal IGF-1 correlates negatively but fetal IGF-1 correlates positively with the length of gestation. This may imply a feedback mechanism or physiological process of maternal restriction. Maternal restriction refers to the limitation of fetal overgrowth by maternal size, uterine size, and nutrient availability [13, 14].

As for the present study, insulin, IGF-1 and IGFBP-3 levels in maternal serum and umbilical cord were significantly higher in the LGA newborns than in the SGA newborns. In addition, both maternal serum and umbilical cord concentrations of IGF-1 and IGFBP-3 correlate with weight, length, head circumference, and abdominal circumference of the newborn. However, insulin concentrations did not significantly correlate with neonatal anthropometry. Such discrepancy may be attributed to the small cohort size and the inconsistencies in the measurement of serum insulin levels. Another possible explanation is the existence of mild hyperglycemia in mothers who are known to be without gestational diabetes or impaired glucose intolerance.

The Pedersen hypothesis proposes that maternal hyperglycemia induces an excessive supply of nutrients which causes fetal hyperinsulinemia and subsequent fetal macrosomia in diabetic pregnancies [19]. Therefore, it would be prudent to assume that fetal weight might be affected by even a limited degree of maternal hyperglycemia, which is still considered to be within the normal range [20]. Unfortunately, data related with maternal serum and umbilical cord glucose concentrations are absent. This absence can be considered as a power limiting factor for

the present study. Another factor that limits the power of the present study is the lack of data related with maternal and fetal levels of growth hormone and subgroup analysis in the LGA group (e.g. symmetric vs asymmetric).

Serum concentrations of ghrelin are higher in patients with anorexia nervosa than in healthy controls. This finding indicates anorexia nervosa is also associated with high concentrations of growth hormone and low concentrations of IGF-1, suggesting nutritionally acquired growth hormone resistance [12]. It has been reported that maternal ghrelin is easily transferred to the fetal circulation and then prompts fetal growth through direct stimulation of cell proliferation in the second half of pregnancy [21].

Recently gathered evidence showing that ghrelin directly stimulates bone formation also supports the anabolic effects of ghrelin on the fetus [22]. Chiesa et al. also declared that maternal ghrelin concentrations were positively associated with neonatal head circumference (and therefore brain development) [14]. This study also claimed that ghrelin concentrations in maternal serum and umbilical cord increased significantly in LGA newborns when compared to the SGA newborns. However, this study was unable to achieve a significant correlation between ghrelin values and neonatal anthropometry. This failure may be due to the small cohort size and the variances in the measurement of serum ghrelin levels. Another reason may be the fact that modes of delivery that elicit stressful stimuli and prolonged active labor can decrease maternal ghrelin concentrations. Much alike, intrapartum fetal distress may lead to a decrease in the ghrelin levels of the newborns [14, 23].

In conclusion, the present study has detected significant relationships between neonatal anthropometry and metabolic and endocrine factors. Fetal macrosomia is found to be associated with increased insulin, IGF-1, IGFBP-3, and ghrelin concentrations in both maternal serum and umbilical cord. However, the power of the present study is limited by the relatively small cohort size, the lack of data related with maternal body weight and height, the absence of data indicating maternal serum and umbilical cord glucose levels, and the lack of subgroup analysis with respect to symmetric and asymmetric LGA.

Further research is needed to optimize the understanding of the mechanisms by which endocrine and metabolic factors may regulate fetal growth.

Competing interests

The authors declare that they have no competing interests.

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